requirement to elect a single probe. New claims 13 and 17 find support at Specification page 7, lines 11-23. New claims 14 and 18 find support in the Specification at page 13, line 30 and Table 1. New claim 15 finds support at Specification page 21, lines 31-33. New claims 16 and 19 find support in original claim 3 and Specification Table 3. Support for new claims 20-26 is found at Specification page 7, lines 11-23; page 8, line 35 through page 9, line 24; page 12, lines 24-27; and Table 3. Support for new claim 27 is found at Specification page 21, lines 15-21.

The claims are amended in response to the Restriction Requirement so as to clarify that they form a single inventive concept in accordance with the requirements of PCT Rule 13.1. A complete copy of all pending claims, including marked up versions of the amended claims is attached hereto.

**III. Detailed response to the restriction requirement**

In the Restriction Requirement the Examiner asserted that the claims comprised the following three groups:

Group I: Claims 1-9 and 12 drawn to a method for determining the susceptibility of HIV to antiviral drugs including probes and a kit.

Group II: Claim 10 drawn to a nucleic acid.

Group III: Claim 11 drawn to a primer pair.

The Examiner, therefore, required that Applicant elect a single invention. The Examiner has further stated that "[i]f [Group] I is elected, then one SEQ ID# for the probe must be elected."

Applicant respectfully traverses the restriction to one elected SEQ ID NO. for the probe. Applicant elects to proceed with the claims of Group I, but objects to the election of one probe in

connection with the elected method and kit claims. Applicant has complied with the election of one probe for examination in connection with claim 9, which is drawn to probes per se.

In the Restriction Requirement, the Examiner stated that

> [t]he inventions listed as Group I part A do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2, they lack the same or corresponding technical features for the following reasons. Group I is directed to a method for determining the susceptibility to antiviral drugs of HIV. However, because Eastman (1998, J Virol. 72(6) pages 5154-5164, in IDS) teaches that HIV resistance to drugs is associated with genotypic changes and teaches probes that can be used to detect changes including at least one codon position in claim 1 C), no special technical feature exists for Group I as defined by PCT Rule 13.2, because it does not define a contribution over the prior art. The technical features of the part B nucleic acids are drawn to probes with different sequences so not sharing the same structure or properties as each other and that the different probes are not related because they detect different mutations, which do not require each other for their practice and do not share the same or a corresponding technical feature.

Paragraph bridging pages 2 and 3 of the instant Office Action. Applicant respectfully traverses.

Firstly, Applicant emphasizes that the elected claims, Group I, are drawn to a method and kit for determining the susceptibility of HIV to antiviral drugs, not to specific nucleotide sequences (save for claim 9). Chapter 800 of the MPEP states that: "[w]here claims of an application define the same essential characteristics of a *single* disclosed embodiment of an invention, restriction therebetween should never be required. This is because the claims are but different definitions of the same disclosed subject matter, varying in breadth or scope of definition." MPEP §806.03 (emphasis added).

Applicant asserts that, as recited in MPEP §806.03, the currently pending method and kit claims all define the same essential characteristics of a single embodiment of the invention which provides for an HIV genotyping assay/method (*see* pages 3 and 4 of the specification) of the protease gene. The recitation of select SEQ ID NOs for representative probes (dependent claims

3, 16, 19, 21 and 23) merely defines the invention in varying breadth or scope; but nonetheless all of the probes listed in claim 3, 16, 19, 21 and 23 share a novel technical feature of the claimed invention. All the probes listed in claim 3, 16, 19, 21 and 23 are capable of simultaneously and specifically hybridizing under the same hybridization and wash conditions to their respective target sequences selected from the group consisting of codon 30; codon 46 and/or 48; codon 50; codon 54; codon 82 and/or 84; and codon 90. Further all the probes of claims 3, 16, 19, 21 and 23 share the common features of being 10 to 25 bases in length, have a Tm of between 36°C and 44°C and are capable of hybridizing to their respective target sequences under stringent hybridization conditions run at 39°C. Consequently, Applicant respectfully requests that restriction of the group I method, kit and composition claims to individual probes be withdrawn as improper, in view of MPEP 806.03.

Applicant further contends that restriction of the method, kit and composition claims to individual probes eviscerates and perverts the concept of Applicants invention, dividing it into pieces which do not properly reflect the synergism and economy provided by the invention as disclosed and claimed in Claims 1 and 12, in violation of MPEP 806.03.

Moreover, Applicant believes that, in the instant application, such restriction runs contrary to the mandate of 35 U.S.C. §112, second paragraph, which recites: "[t]he specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. §112, second paragraph (emphasis added). It is Applicants position that limitation of the instant invention to the use of one or two probes impinges on Applicant's ability to fully comply with §112, second paragraph, for the reasons described above. Specifically, the probes of SEQ ID NOs 7 to 477 found in claims 3, 16, 19, 21 and 23 are all capable of simultaneously and specifically hybridizing under

the same hybridization and wash conditions to their respective target sequences. Therefore such restriction is contrary to the statute and improper in the instant application.

With regard to the group I invention's alleged lack of a special technical feature, Applicant asserts that the amendment of claim 1 to recite the use of "at least two probes ... wherein said probes are immobilized on a solid support" provides a special technical feature over the cited art. Eastman *et al.* neither teaches nor suggests the use of at least two probes immobilized on a solid support. Consequently, as amended the currently pending claims comprise a special technical feature which links the pending claims so as to form a single general inventive concept, thereby fulfilling the requirements for unity of invention under PCT Rule 13.

Notwithstanding the foregoing, in compliance with the Examiner's requirement and the conditions of 37 C.F.R. § 1.143, in response to the restriction requirement that the Examiner imposed, Applicant elects, with traverse, to prosecute claims 1-9, and 12, *i.e.*, the Group I claims. Further with respect to claim 9, Applicant provisionally elects as a probe SEQ ID NO:267, said probe is directed to target sequence codon 82 and/or 84.

## IV. Conclusion

Applicant believes that the current Response is in full compliance with the requirements set out in the instant Restriction Requirement. In view of the foregoing Amendment and Remarks, Applicant respectfully requests reconsideration and withdrawal of the Restriction Requirement with respect to a single probe in connection with the elected method and kit claims.

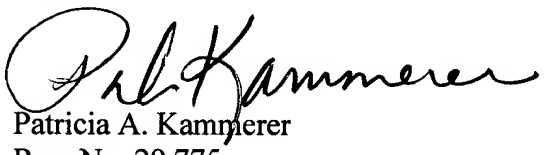
**Request for Interview**

The undersigned applicant's representative has made several attempts since November 8, 2002 to set up a telephone interview with Examiner M. Hill in an effort to discuss the required

restriction to one probe. Examiner Hill returned the several telephone calls but reported that he was unable to set up an interview that would necessarily include his supervisor. Finally in a voicemail message left November 25, Examiner Hill reported that the case had been transferred to group 1634 to Examiner Gary Williams at (703) 308-1152. The undersigned has not been able to reach Examiner Williams to date.

In order to facilitate prosecution of this application, Applicants request that the new examiner give the undersigned attorney a call at (713) 787-1438 to discuss the restriction requirement before any final determination is made.

Respectfully submitted,



Patricia A. Kammerer
Reg. No. 29,775
Attorney for Assignee
INNOGENETICS N.V.

HOWREY SIMON ARNOLD & WHITE, LLP
750 Bering Drive
Houston, Texas 77057-2198
(713) 787-1400

Date: November 26, 2002

## MARKED-UP VERSION OF CLAIM AMENDMENTS

1. **(Amended)** Method for determining the susceptibility to antiviral drugs of HIV viruses in a biological sample, with said method comprising:

a) if need be, releasing, isolating or concentrating the polynucleic acids present in the sample;

b) if need be amplifying the relevant part of ~~the~~ a protease gene of HIV with at least one suitable primer pair;

c) hybridizing the polynucleic acids of step a) or b) with at least two ~~one of the following probes:~~

probes specifically hybridizing to a target sequence of the HIV protease gene, said target sequence selected from the group consisting of ~~comprising~~ codon 30;

~~probes specifically hybridizing to a target sequence comprising~~ codon 46 and/or 48;

~~probes specifically hybridizing to a target sequence comprising~~ codon 50;

~~probes specifically hybridizing to a target sequence comprising~~ codon 54;

~~probes specifically hybridizing to a target sequence comprising~~ codon 82 and/or 84;

~~probes specifically hybridizing to a target sequence comprising~~ codon 90;

or the complement of said probe;

~~further characterized in that~~ wherein said probes specifically hybridize to any of the target sequences presented in figure 1, or Table 3, or to the complement of said target sequences;

wherein said probes are capable of simultaneously hybridizing to their respective targets under appropriate hybridization and wash conditions;

wherein said probes are immobilized on a solid support; and

d) inferring from the result of step c) whether or not a mutation giving rise to drug resistance is present in any of said target sequences.

3. **(Amended)** Method according to claim 1 ~~2~~, further characterized in that said probes are chosen from the following list: SEQ ID NO: 7 to SEQ ID NO: 477, SEQ ID NO: 510 to SEQ ID NO: 519 or the complement of said probes.

4. Method according to claim 1 further characterized in that said primer pair is chosen from the following primers: SEQ ID NO: 3, SEQ ID NO: 503, SEQ ID NO: 504, SEQ ID NO: 4, SEQ ID NO: 506, SEQ ID NO: 507, SEQ ID NO: 508 and SEQ ID NO: 509.

5. **(Amended)** Method according to claim 1 further characterized in that:

step b) comprises amplifying a fragment of the protease gene with at least one 5'-primer specifically hybridizing to a target sequence located at nucleotide position 210 to 260 of the protease gene, in combination with at least one suitable 3'-primer, and

step c) comprises hybridizing the polynucleic acids of step a) or b) with at least ~~one~~ **two** of the probes specifically hybridizing to a target sequence or its complement, comprising codon 90.

6. **(Amended)** Method according to claim 1 further characterized in that:

step b) comprises amplifying a fragment of the protease gene with at least one 3'-primer specifically hybridizing to a target sequence located at nucleotide position 253 (codon 85) to position 300, in combination with at least one suitable 5'-primer, and

step c) comprises hybridizing the polynucleic acids of step a) or b) with at least ~~one~~ **two** of the probes specifically hybridizing to a target sequence or its complement, comprising any of codons 30, 46, 48, 50, 52, 54, 82 and 84.

7. Method according to claim 5, further characterized in that the 5'-primer is SEQ ID NO: 5 and the 3'- primer is one primer or a combination of primers chosen from the following primers: SEQ ID NO: 4, SEQ ID NO: 506, SEQ ID NO: 507, SEQ ID NO: 508 and SEQ ID NO: 509.

8. Method according to claim 6, further characterized in that the 5'-primer is one primer or a combination of primers chosen from the following primers: SEQ ID NO: 3, SEQ ID NO: 503, SEQ ID NO: 504 and the 3'-primer is SEQ ID NO: 6.

9. **(Amended)** A probe as defined in claim 1 for use in a method for determining the susceptibility to antiviral drugs of HIV viruses in a biological sample**, comprising SEQ ID NO: 267.**

12. **(Amended)** A diagnostic kit enabling a method for determining the susceptibility to antiviral drugs of HIV viruses in a biological sample, with said kit comprising:

a) when appropriate, a means for releasing, isolating or concentrating the polynucleic acids present in said sample;

b) when appropriate, at least one of the primers comprising SEQ ID NO: 3, SEQ ID NO: 503, SEQ ID NO: 504, SEQ ID NO: 4, SEQ ID NO: 506, SEQ ID NO: 507, SEQ ID NO: 508 or SEQ ID NO: 509; or

a 5'-primer specifically hybridizing to a target sequence located at nucleotide position 210 to 260 of the protease gene; or

a 3'-primer specifically hybridizing to a target sequence located at nucleotide position 253 (codon 85) to 300 of the protease gene;

c) at least ~~one of the probes of claim 1 possibly~~ two probes that specifically and simultaneously hybridize to a target sequence of HIV protease gene, said target sequence selected from the group consisting of codon 30, codon 46 and/or 48, codon 50, codon 54, codon 82 and/or 84, codon 90, fixed to a solid support, wherein said probes are capable of simultaneously hybridizing to their respective targets under appropriate hybridization and wash conditions;

d) a hybridization buffer, or components necessary for producing said buffer;

e) a wash solution, or components necessary for producing said solution;

f) when appropriate, a means for detecting the hybrids resulting from the preceding hybridization;

g) when appropriate, a means for attaching said probe to a solid support.

13. **(New)** The method according to claim 1, wherein at least two probes are provided for hybridizing to each of the target sequences of codon 30; codon 46 and/or 48; codon 50; codon 54; codon 82 and/or 84; or codon 90.

14. **(New)** The method according to claim 13, wherein said probes are between 10 and 25 nucleotides in length and have a Tm between 36°C and 44°C.

15. **(New)** The method according to claim 13, wherein said probes are capable of hybridizing to their respective target sequences under stringent hybridization conditions carried out at 39°C.

16. **(New)** The method according to claim 15, wherein said probes are selected from the group consisting of SEQ ID NO: 7 to SEQ ID NO: 477, SEQ ID NO: 510 to SEQ ID NO: 519 and the complements thereof.

17. **(New)** The kit according to claim 12, wherein at least two probes are provided for hybridizing to each of the target sequences of codon 30; codon 46 and/or 48; codon 50; codon 54; codon 82 and/or 84; or codon 90.

18. **(New)** The kit according to claim 17, wherein said probes are between 10 and 25 nucleotides in length and have a Tm between 36°C and 44°C.

19. **(New)** The kit according to claim 17, wherein said probes are selected from the group consisting of SEQ ID NO: 7 to SEQ ID NO: 477, SEQ ID NO: 510 to SEQ ID NO: 519 and the complements thereof.

20. **(New)** A solid support for use in the method of claim 1, said support having two or more probes immobilized thereon, wherein said probes are capable of specifically and simultaneously hybridizing to a target sequence of the HIV protease gene, said target sequence selected from the group consisting of codon 30, codon 46 and/or 48, codon 50, codon 54, codon 82 and/or 84, codon 90 and the complement thereof.

21. **(New)** The solid support of claim 20 wherein the probes are selected from the group consisting of SEQ ID NOs. 7-477.

22. **(New)** The solid support of claim 20 wherein at least two probes are specific for codon 82.

23. **(New)** The solid support of claim 22 wherein the probes are selected from the group consisting of SEQ ID. NOs. 228-357.

24. **(New)** The solid support of claim 22 comprising SEQ ID NO. 267 and SEQ ID NO. 354.

25. **(New)** The solid support of claim 20 comprising at least two probes for each target sequence of codon 30, codon 46 and/or 48, codon 50, codon 54, codon 82 and/or 84, and codon 90.

26. **(New)** A composition comprising at least two probes fixed to a solid support for use in the method of claim 1, wherein said probes are capable of specifically and simultaneously hybridizing to a target sequence of the HIV protease gene, said target sequence selected from the group consisting of codon 30, codon 46 and/or 48, codon 50, codon 54, codon 82 and/or 84, codon 90 and the complement thereof.

27. **(New)** The composition of claim 26, wherein the probes are further provided with a poly-T-tail.